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Glenn P. Ladwig, Patent Attorney, Reg. No. 46,853

REQUEST FOR CERTIFICATE OF  
CORRECTION UNDER 37 CFR 1.322  
Docket No. USF.182XC1  
Patent No. 7,595,303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Shyam S. Mohapatra, Mukesh Kumar  
Issued : September 29, 2009  
Patent No. : 7,595,303  
Conf. No. : 6872  
For : Genetic Adjuvants for Immunotherapy

Mail Stop Certificate of Corrections Branch  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION  
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

**Patent Reads:**Title Page, (57) Abstract, line 13:

“cells generally modified”

Column 3, line 32:

“a, airway,”

Column 7, line 9:

“parental administration”

Column 9, line 38:

“ctgtcaatta”

Column 9, line 54:

“ttttactgaa”

Column 10, line 5:

“YKTKLHA”

Column 33, lines 61-62:

“recombinant, nucleotides,”

**Application Reads:**Page 37, line 10:

--cells genetically modified--

Page 4, line 29:

--a, airway;--

Page 10, line 18:

--parenteral administration--

Page 14, line 8:

--ctgtgcctta--

Page 14, line 16:

--ttttcatgaa--

Page 14, lines 26-27:

--YKTKIKLCILLHA--

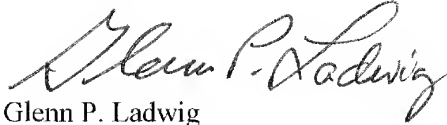
Amendment Under 37 CFR § 1.111 dated June 26, 2007 (original claim 15, renumbered as claim 8):

--recombinant nucleotides,--

A true and correct copy of pages 4, 10, 14, and 37 of the specification as filed and the Amendment Under 37 CFR § 1.111 dated June 26, 2007 which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



Glenn P. Ladwig

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Gainesville, FL 32614-2950

GPL/jnw

Attachments: Copy of pages 4, 10, 14, and 37 of the specification  
Copy of Amendment Under 37 CFR § 1.111 dated June 26, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,595,303

Page 1 of 1

APPLICATION NO.: 10/655,873

DATED : September 29, 2009

INVENTOR : Shyam S. Mohapatra, Mukesh Kumar

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, (57) Abstract,

Line 13, "cells generally modified" should read --cells genetically modified--.

Column 3,

Line 32, "a, airway;" should read --a, airway;--.

Column 7,

Line 9, "parental administration" should read --parenteral administration--.

Column 9,

Line 38, "ctgtcaatta" should read --ctgtgcctta--.

Line 54, "ttttactgaa" should read --ttttcatgaa--.

Column 10,

Line 5, "YKTKLHA" should read --YKTKIKLCILLHA--.

Column 33,

Lines 61-62, "recombinant, nucleotides," should read --recombinant nucleotides,--.

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immunization with alum and KBG allergen, their serum was analyzed for total IgE (Figure 2B) and KBG-specific IgG2a and IgG1 (Figure 2A) antibodies by ELISA. Bars represent the means  $\pm$  SDs.  $*P < .05$ ;  $**P < .01$ ;  $***P < .001$  in comparison with pcDNA3.1 group.  $^{\dagger}P < .05$ ;  $^{\ddagger}P < .01$ ;  $^{\text{††}}P < .001$  in comparison with pIFN- $\gamma$ .  $^{\ddagger}P < .05$ ;  $^{\text{††}}P < .01$ ;  $^{\text{†††}}P < .001$  in comparison with pIL-12 group.

Figures 3A-3C show analysis of cytokine production and dominant cytokine pattern following cytokine-encoding DNA vaccination. Figures 3A and 3B show analysis of cytokine production. Mice ( $n = 6$ ) were vaccinated as described in the Methods section. On day 7 after KBG and alum immunization, their spleens were cultured *in vitro* for 48 hours in the presence of KBG allergen and cytokines were measured by ELISA. Bars represent the means  $\pm$  SDs.  $*P < .05$ ;  $**P < .01$ ;  $***P < .001$  in comparison with pcDNA3.1 group.  $^{\dagger}P < .05$ ;  $^{\ddagger}P < .01$ ;  $^{\text{††}}P < .001$  in comparison with pIFN- $\gamma$  (*IFN-g*) group.  $^{\ddagger}P < .05$ ;  $^{\text{††}}P < .01$ ;  $^{\text{†††}}P < .001$  in comparison with pIL-12 (*IL-12*) group. Figure 3C shows analysis of the dominant cytokine pattern after cytokine DNA vaccination. Dominant cytokine pattern was determined from the IFN- $\gamma$ /IL-4 and IL-2/IL-4 ratios. Bars represent means.

Figure 4 shows measurement of the airway hyperresponsiveness in KBG-sensitized and -challenged mice after cytokine DNA vaccination. Naive mice ( $n = 4$ ) were vaccinated as described in the Methods section and sensitized with the allergen 7 days later. Ten days after the sensitization, animals were challenged intranasally 3 times with 50  $\mu$ g of KBG allergen. Airway reactivity to inhaled methacholine (6 to 50 mg/mL) was measured 24 hours later. Results are expressed as means  $\pm$  SDs of enhanced pause values. *a*,  $P < .05$ ; *aa*,  $P < .01$  in comparison with pcDNA3.1 group. *b* and *c*,  $P < .05$  in comparison with pIFN- $\gamma$  (*IFN-g*) and pIL-12 (*IL-12*) groups, respectively.

Figures 5A-5D show assessment of the lung inflammation in KBG-sensitized and -challenged mice after cytokine DNA vaccination. Lung tissue was removed from the different groups of mice ( $n = 4$ ) 24 hours after the last intranasal allergen challenge and was stained with hematoxylin and eosin. A representative photomicrograph from each group is shown (Figure 5A: pcDNA3.1; Figure 5B: pIFN- $\gamma$ ; Figure 5C: pIL-12; Figure 5D: pIFN- $\gamma$  + pIL-12). Arrows indicated cellular infiltration. *a*, airway; *v*, vessel.

within one vector (e.g., a DNA plasmid) or separate vectors (e.g., separate plasmids), or types of vectors. Optionally, the pharmaceutical composition of the present invention further includes an antigen.

5 The pharmaceutical compositions of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Furthermore, as used herein, the phrase "pharmaceutically acceptable carrier" means any of the standard pharmaceutically acceptable carriers. The pharmaceutically acceptable carrier can include diluents, adjuvants, and vehicles, as well as implant carriers, and inert, non-toxic solid or liquid fillers, diluents, or encapsulating material that does not react with the active  
10 ingredients of the invention. Examples include, but are not limited to, phosphate buffered saline, physiological saline, water, and emulsions, such as oil/water emulsions. The carrier can be a solvent or dispersing medium containing, for example, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. Formulations are described in a number of sources that are well  
15 known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Sciences* (Martin EW [1995] Easton Pennsylvania, Mack Publishing Company, 19<sup>th</sup> ed.) describes formulations which can be used in connection with the subject invention. Formulations suitable for parenteral administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes  
20 which render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for  
25 injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, tablets, *etc.* It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the subject invention can include other agents conventional in the art having regard to the type of formulation in question. The pharmaceutical composition can be adapted for various forms of

241 agccaccgcc ctcacctgcc gcggccacag gtctgcatcc agcggcgcgc cctgtgtccc  
 301 tgcagtgccg gctcagcatg tgcacagcgc gcagcctcct cctgtggct accctggctc  
 361 tcttgacca cctcagtttg gccagaaacc tccccgtggc cactccagac ccaggaatgt  
 421 tcccagcct tcaccactcc caaacctgc tgaggggcgt cagcaacatg ctccagaagg  
 5 481 ccagacaaac tctagaattt tacccttgca cttctgaaga gattgatcat gaagatatca  
 541 caaaagataa aaccagcaca gtggaggcct gtttaccatt ggaattaacc aagaatgaga  
 601 gttgcctaaa ttccagagag acctctttca taactaatgg gagttgcctg gcctccagaa  
 661 agacctcttt tatgatggcc ctgtgcctta gtagtattta tgaagacttg aagatgtacc  
 721 aggtggagtt caagaccatg aatgcaaagc ttctgatgga tccaaaggagg cagatctttc  
 10 781 tagatcaaaa catgctggca gttattgatg agctgatgca ggccctgaat tcaacagtg  
 841 agactgtgcc acaaaaatcc tccctgaag aaccggattt ttataaaact aaatcaagc  
 901 tctgcatact tcttcagctt tcagaattc gggcagtgac tattgataga gtgatgagct  
 961 atctgaatgc ttctaaaaa gcgagggtccc tccaaaccgt tgcattttt ataaaacttt  
 1021 gaaatgagga aactttgata ggatgtggat taagaactag ggagggggaa agaaggatgg  
 15 1081 gactattaca tccacatgat acctctgac aagtatttt gacatttact gtggataaat  
 1141 tgttttaag tttcatgaa tgaattgcta agaagggaaa ataccatcc tgaaggtgtt  
 1201 ttcatctcac ttaatagaa gggcaaataa ttataagcta ttctgtacc aaagtgtttg  
 1261 tggaacaaaa catgtaagca taacttattt taaaatattt attatataa cttggtaatc  
 1321 atgaaagcat ctgagctaac ttatattat ttatgttata ttattaaat tatttatcaa  
 20 1381 gtgtatttga aaaatattt taagtgttct aaaaataaaa gtattgaatt aaagtgaaaa  
 1441 aaaa (SEQ ID NO:7)

MWPPGSASQPPSPAAATGLHPAARPVSLQCRLSMCPARSLLLVATLVLLDHLSLAR  
 NLPVATPDPGMFPCLLHHSQNLLRAVSNNMLQKARQTLEFYPTCTSEEDHEDITKDKTS  
 25 TVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEF  
 KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFDYKTKIKL  
 CILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO:8)

A further exemplified nucleotide sequence encodes the human IL-12 p40 subunit  
 30 (Accession No: NM\_002187, NCBI database, which is hereby incorporated by reference in  
 its entirety):

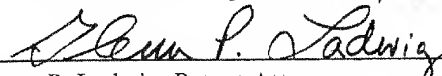
1 ctgtttcagg gccattggac tctccgtcct gccagagca agatgtgtca ccagcagttg  
 61 gtcactctct gggtttccct gggtttctg gcactcctcc tegtggccat atgggaactg  
 35 121 aagaagatg ttatgtcgt agaattgat tggatccgg atgccctgg agaaatggtg  
 181 gtctcaccct gtgacacccc tgaagaagat ggtatcacct ggaccttga ccagagcagt  
 241 gaggtcttag gctctggcaa aacctgacc atccaagta aagagtttg agatgctggc  
 301 cagtacacct gtcacaaagg aggcgaggtt ctaagccatt cgctcctgct gcttcacaaa  
 361 aaggaagatg gaattggct cactgatatt taaaggacc agaaagaacc caaaaataag  
 40 421 acctttctaa gatcgagagc caagaattat tctggacgtt tcacctgctg gtggctgacg  
 481 acaatcagta ctgatttgac attcagtgtc aaaagcagca gaggtctctc tgaccccaaa  
 541 ggggtgacgt gcggagctgc tacactctct gcagagagag tcagagggga caacaaggag

Abstract

The present invention pertains to methods and pharmaceutical compositions for modulating an immune response. The method of the present invention involves administration of an effective amount of nucleic acid molecules encoding interleukin-12 (IL-12), interferon-gamma (IFN- $\gamma$ ), or a combination thereof, to a patient in need of such treatment. The pharmaceutical compositions of the invention contain nucleic acid molecules encoding IL-12 and/or IFN- $\gamma$  and an operably-linked promoter sequence. In another aspect, the present invention concerns expression vectors containing a nucleotide sequence encoding IL-12 and IFN- $\gamma$ , and an operably-linked promoter sequence. In another aspect, the present invention concerns cells genetically modified with a nucleotide sequence encoding IL-12 and IFN- $\gamma$ .



I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on June 26, 2007.

  
Glenn P. Ladwig, Patent Attorney

AMENDMENT UNDER 37 C.F.R. §1.111  
Examining Group 1632  
Patent Application  
Docket No. USF-182XC1  
Serial No. 10/655,873

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Marcia Stephens Noble  
Art Unit : 1632  
Applicants : Shyam S. Mohapatra, Mukesh Kumar  
Serial No. : 10/655,873  
Filed : September 5, 2003  
Confirm. No. : 6872  
For : Genetic Adjuvants for Immunotherapy

MS AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.111

A Petition and fee for a one-month Extension of Time through and including June 26, 2007, accompanies this Amendment.

In response to the Office Action dated February 26, 2007, please amend the above-identified application as follows:

In the Specification

Please replace the paragraphs found on page 16, lines 21-32 through page 17, lines 1-16 of the specification with the following paragraphs:

An exemplified nucleotide sequence encodes human IFN- $\gamma$  (Accession No: NM\_000639, NCBI database, which is hereby incorporated by reference in its entirety):

```

1 tgaagateng ctattagaag agaaagatac gtnaagteet ttggaectga teagettgat
61 acaagaaeta ctgatttcaa ettetttgcg ttaattctet cggaaaacat gaaatataca
121 agttatatet tggettitea getetgata gttttgggtt ctottggetg ttaetgecag
181 gacecatatg taaaagaage agaaaacett aagaaatatt ttaatgcagg teatcagat
241 gtageggata atggaaactt ttcttagge attttgaaga attggaaaga ggagagtga
301 agaaaaataa tgcagageca aattgtetec tttaacttca aactttttaa aaacttttaa
361 gatgaacaga gatacaaaaa gattgtggag accataaagg aagaatgaa tgcgaagttt
421 ttenatagea acaaaaagaa acgagatgac ttgaaaaage tgactaatta ttgggtaact
481 gaettgaatg tcaaaegcaa ageaataent gaactatcc aagtgatgag tgaactgtcg
541 ccageageta aaacagggaa gggaaaaagg agteagatgc tgttcaagg tgaagagea
601 tcccagtaat ggttgctctg cctgaatat ttgaattta aatataaate tatttattaa
661 tatttaacat tatttatatg gggatatat tttagactc ataatcaaa taagtattta
721 taatagaaac ttgtgtgtaa tgaanaagaa tatatattaa tatatgtati atttataatt
781 cctatactct gtgaactgtc caettaatcc ttgttttct gaataattag gcaaggetat
841 gtgattacaa ggetttatct cagggggeaa etaggengce aaactaaga agateccatg
901 ggttgtgtgt ttattcaact tgatgataca atgaacaact ataagtgaag tgatactate
961 cagttaetgc cggtttgaaa atatgeetgc aatetgagcc agtgetttta tggeatgta
1021 gacagaactt gaattgtgta ggtgaacctg atgaaaacat agcatctcag gagatttcat
1081 geetgggtgt tcaaatattt gttgaacact gtgaactgac ccaantggaa agtaactcat
1141 ttgttaaaat tacaataate taatatatat gaataaagtg taagticaca act (SEQ ID NO:11)

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MKYTSYILAFQLCIVLGS LGCYCQDPYVKEAENLKKYFNAGHSDVADNGTLFLGILKNW  
KEESDRKIMQSQIVSFYTKLFKNFKDDQSIQKSVETIKEDMNVKFFNSNKKKRDDFEKLT  
NYSVTDLNVQRKAHELIVQMAELSPA AKTGKRKRSQMLFQ GRRASQ (SEQ ID NO:12)

A further exemplified nucleotide sequence encodes human IFN- $\gamma$  (Accession No. NM\_000619), NCBI database, which is hereby incorporated by reference in its entirety):

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1 cacattgttc tgatcatctg aagatcagct attagaagag aaagatcagt taagtccttt
61 ggacctgac agcttgatac aagaactact gatttcaact tctttggctt aattctctcg
121 gaaacgatga aatatacaag ttatatcttg gcttticagc tctgcatcgt ttgggttct
181 ctggctgtt actgccagga cccatatgta aaagaagcag aaaaccttaa gaaatatttt
241 aatgcaggtc attcagatgt agcggataat ggaactcttt tcttaggcat ttgaagaat
301 tggaaagagg agagtgcacg aaaaataatg cagagccaaa ttgtctcctt ttacttcaaa

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361 cttttaaaa actttaaga tgaccagagc atccaaaaga gtgtggagac catcaaggaa  
 421 gacatgaatg tcaagtttt caatagcaac aaaaagaaac gagatgactt cgaaaagctg  
 481 actaattatt cgtaactga ctggaatgc caacgcaaag caatacatga actcatccaa  
 541 gtgatggctg aactgtgcc agcagctaaa acagggaagc gaaaaaggag tcagatgctg  
 601 tttcgaggtc gaagagcalc ccagtaatgg ttgtcctgcc tgcaatatt gaattttaa  
 661 tctaaatcta ttattaata ttaacattt ttatatggg gaatatatt ttagactcal  
 721 caatcaaata agtatttata atagcaactt ttgtgaatg aaaatgaata tctattaata  
 781 taigtatlat ttataattcc tatacctgt gactgtctca cttaacctt tgtttctga  
 841 ctaattaggc aaggctatgt gattacaagg ctttatctca ggggccaaact aggcagccaa  
 901 cctaagcaag atcccatggg ttgtgtgtt atttacttg atgatacaat gaacacttat  
 961 aagtgaagtg atactatcca gtactgccg gtltgaaaat atgcctgcaa tctgagccag  
 1021 tgctttaatg gcatgtcaga cagaactga atgtgtcagg tgacctgat gaaaacatag  
 1081 catctcagga gatttcatgc ctggtgcttc caaatattgt tgacaactgt gactgtaccc  
 1141 aatggaaag taactcattt gttaaaatta tcaatacta atatatatga ataaagtga  
 1201 agttcacac aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa (SEQ ID NO: 11)

The corresponding amino acid sequence for human IFN- $\gamma$  (Accession No. NP\_000610 ),  
NCBI database, is hereby incorporated by reference in its entirety):

1 MKYTSYILAF QLCIVLGS LG CYCQDPYVKE AENLKKYFNA GHSDVADNGT LFLGILKNWK  
 61 EESDRKIMQS QIVSFYFKLF KNFKDDOSIQ KSVETIKEDM NVKFFNSNKK KRDDFEKLTN  
 121 YSVTDLNVQR KAIHELIOVM AELSPA AKTG KRKRSOMLFR GRRASQ (SEQ ID NO:12)

In the Claims

Claim 1 (Currently amended): A method for modulating an immune response, comprising co-administering to a patient:

an effective amount of a nucleic acid sequence encoding p35 and p40 subunits of human IL-12, and an operably linked a promoter sequence operably linked to the nucleic acid sequence encoding the p35 and p40 subunits; and

an effective amount of a nucleic acid sequence encoding human IFN- $\gamma$ , and an operably linked a promoter sequence operably linked to the nucleic acid sequence encoding human IFN- $\gamma$ ; and

an antigen such that the co-administering results in an increase of Th1-type cytokine production, an increase of IgG2a-levels specific to the antigen, a decrease of Th2-type cytokine production, and reduced serum IgE-levels.

Claim 2 (Cancel)

Claim 3 (Currently amended): The method of claim 1, wherein the administering step includes selecting the co-administering IL-12 to comprise a p35 subunit and a p40 subunit, results in expression of the p35 and the p40 subunits, the p35 subunit to comprise an comprising the amino acid sequence of SEQ ID NO:8, and the p40 subunit to comprise an comprising the amino acid sequence of SEQ ID NO:10.

Claims 4-5 (Cancelled)

Claim 6 (Currently amended): The method of claim 1, wherein the administering step includes selecting the co-administering IFN- $\gamma$  results in expression of the human IFN- $\gamma$ , and wherein the human IFN- $\gamma$  comprises the to comprise an amino acid sequence of SEQ ID NO:12.

Claim 7 (Currently amended): The method of claim 1, wherein ~~the administering step includes selecting~~ the nucleic acid sequence ~~encoding~~ encoding the p35 and the p40 subunits of the human IL-12 to comprise comprises SEQ ID NO:7 and SEQ ID NO:9.

Claim 8 (Currently amended): The method of claim 1, wherein ~~the administering step includes selecting~~ the nucleic acid sequence ~~encoding~~ encoding the human IFN- $\gamma$  to comprise comprises SEQ ID NO:11.

Claim 9 (Previously presented): The method of claim 1, wherein the nucleic acid sequences are administered with a pharmaceutically acceptable carrier.

Claim 10 (Cancelled)

Claim 11 (Previously presented): The method of claim 1, wherein the nucleic acid sequences are administered within separate DNA plasmids.

Claim 12 (Previously presented): The method of claim 1, wherein the nucleic acid sequences and promoter sequences are administered within a viral vector.

Claims 13-14 (Cancelled)

Claim 15 (Currently amended): The method of ~~claim 14~~ claim 1, wherein the antigen is selected from the group consisting of a protein, peptide, glycoprotein, carbohydrate, lipid, glycolipid, hapten conjugate, recombinant nucleotides, killed or attenuated organism, toxin, toxoid, and organic molecule.

Claims 16-17 (Cancelled)

Claim 18 (Currently amended): The method of ~~claim 14~~ claim 1, wherein the antigen is administered to the patient with the nucleic acid sequences and a pharmaceutically acceptable carrier.

Claim 19 (Original): The method of claim 1, wherein the patient is human.

Claims 20-42 (Cancelled)

Claim 43 (Currently amended): A method for modulating an immune response, comprising co-administering to a patient:

an effective amount of a plasmid comprising a nucleic acid sequence encoding p35 and p40 subunits of human IL-12, and an operably linked a promoter sequence operably linked to the nucleic acid sequence encoding the p35 and p40 subunits; and

an effective amount of a plasmid comprising a nucleic acid sequence encoding human IFN- $\gamma$ , and an operably linked a promoter sequence operably linked to the nucleic acid sequence encoding the human IFN- $\gamma$ ; and

an antigen, such that the co-administering results in an increase of Th1-type cytokine production, an increase of IgG2a-levels specific to the antigen, a decrease of Th2-type cytokine production, and reduced serum IgE-levels.

Claim 44 (Cancel)

Claim 45 (Currently amended): The method of ~~claim 44~~ claim 43, wherein ~~the administering step includes selecting the antigen to comprise an allergen~~ the antigen comprises an allergen.

Claim 46 (Currently amended): The method of ~~claim 44~~ claim 43, wherein ~~the administering step includes selecting the antigen to comprise~~ the antigen comprises Kentucky blue grass (KBG) allergen extract.

Claim 47 (Currently amended): The method of claim 43, wherein ~~the administering step includes selecting the operably linked promoters to~~ promoter sequences comprise cytomegalovirus (CMV) promoters.

Claim 48 (Currently amended): The method of ~~claim 44~~ claim 43, wherein ~~the administering step includes selecting the antigen to comprise~~ the antigen comprises Kentucky blue grass (KBG) allergen extract, and the operably linked ~~promoters to~~ promoter sequences comprise cytomegalovirus (CMV) promoters.

Claim 49 (Previously presented): The method of claim 43, wherein the patient is human.

Claim 50 (Currently amended): The method of claim 43, wherein ~~the administering step includes selecting the co-administering IL-12 to comprise results in expression of the p35 and the p40 subunits, the p35 subunit comprising the amino acid sequences~~ sequence of SEQ ID NO:8 and SEQ ID NO:10, and ~~the IFN- $\gamma$  to comprise the p40 subunit comprising an~~ the amino acid sequence of ~~SEQ ID NO:12~~ SEQ ID NO:10.

Claim 51 (Cancelled)

Claim 52 (Previously presented): The method of claim 43, wherein the patient suffers from a condition selected from the group consisting of allergy, allergic rhinitis, atopic dermatitis, asthma, allergic sinusitis, pulmonary fibrosis, and cancer.

Claim 53 (Currently amended): The method of claim 43, ~~further comprising administering an antigen to the patient,~~ wherein the plasmids are administered by a route selected from the group consisting of intramuscularly, orally, and intranasally.

Claim 54 (Currently amended): A pharmaceutical composition comprising a plasmid comprising a nucleic acid sequence encoding p35 and p40 subunits of human IL-12, and ~~an operably~~

linked a promoter sequence operably linked to the nucleic acid sequence encoding the p35 and p40 subunits;

a plasmid comprising a nucleic acid sequence encoding human IFN- $\gamma$  and ~~an operably linked~~  
a promoter sequence operably linked to the nucleic acid sequence encoding the human IFN- $\gamma$ ;  
and a pharmaceutically acceptable carrier.

Claim 55 (Currently amended): The pharmaceutical composition of claim 54, wherein ~~said~~  
the composition further comprises an antigen.

Claim 56 (Currently amended): The pharmaceutical composition of claim 55, wherein ~~said~~  
the antigen is an allergen.

Claim 57 (Currently amended): The pharmaceutical composition of claim 54, wherein ~~said~~  
the nucleic acid sequence encoding the p35 and p40 subunits of the human IL-12 comprises results in  
expression of the subunits, wherein the subunits comprise the amino acid sequences of SEQ ID NO:  
8 and SEQ ID NO:10, and wherein ~~said~~ the nucleic acid sequence encoding the human IFN- $\gamma$   
~~comprises the results in expression of the human IFN- $\gamma$ , wherein the human IFN- $\gamma$  comprises the~~  
amino acid sequence of SEQ ID NO:12.

Claim 58 (Currently amended): The method of claim 1, wherein the nucleic acid sequence  
encoding the p35 and p40 subunits of the human IL-12 and the nucleic acid sequence encoding the  
human IFN- $\gamma$  are ~~administered~~ co-administered to the patient through a mucosal route.

Claim 59 (Cancel)

Claim 60 (Currently amended): The method of claim 1, wherein the nucleic acid sequence  
encoding the p35 and p40 subunits of the human IL-12 and the nucleic acid sequence encoding the  
human IFN- $\gamma$  are ~~administered~~ co-administered to the patient intranasally.



Claim 61 (Cancel)

Claim 62 (Currently amended): The method of claim 43, wherein the plasmids are ~~administered~~ co-administered to the patient through a mucosal route.

Claim 63 (Cancel)

Claim 64 (Currently amended): The method of claim 43, wherein the plasmids are ~~administered~~ co-administered to the patient intranasally.

Claim 65 (Cancel)

Claim 66 (Previously presented): The method of claim 1, wherein the patient suffers from a condition selected from the group consisting of allergy, allergic rhinitis, atopic dermatitis, asthma, allergic sinusitis, pulmonary fibrosis, and cancer.

Claim 67 (Cancel)

Claim 68 (Currently amended): The pharmaceutical composition of ~~claim 54~~ claim 55, wherein ~~said~~ the composition increases Th1-type cytokine production, increases IgG2a specific to the antigen, decreases Th2-type cytokine production, and reduces serum IgE *in vivo*.

Claim 69 (New): The pharmaceutical composition of claim 54, wherein the nucleic acid sequence encoding the p35 and p40 subunits of human IL-12 comprises SEQ ID NO: 7 and SEQ ID NO: 9.

Claim 70 (New): The pharmaceutical composition of claim 54, wherein the nucleic acid sequence encoding human IFN- $\gamma$  comprises SEQ ID NO: 11.

Claim 71 (New): The method of claim 43, wherein the nucleic acid sequence encoding the p35 and p40 subunits of human IL-12 comprises SEQ ID NO: 7 and SEQ ID NO: 9.

Claim 72 (New): The method of claim 43, wherein the nucleic acid sequence encoding human IFN- $\gamma$  comprises SEQ ID NO: 11.

Claim 73 (New): The method of claim 1, wherein the nucleic acid sequences are administered by a route selected from the group consisting of intramuscularly, orally, and intranasally.

Remarks

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, 43-50, and 52-68 were pending in the subject application. By this Amendment, claims 1, 3, 6-8, 15, 18, 43, 45-48, 50, 53-58, 60, 62, 64, and 68 have been amended, claims 2, 4, 14, 20, 21, 23-31, 44, 59, 61, 63, 65, and 67 have been cancelled, and new claims 69-73 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 1, 3, 6-9, 11, 12, 15, 18, 19, 43, 45-50, 52-58, 60, 62, 64, 66, and 68-73 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants and the applicants' representative wish to thank Examiners Noble and Paras for the courtesy of the telephonic interview conducted with the undersigned and Mr. Jay Pattumudi on June 12, 2007, regarding the Office Action. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

As an initial matter, the applicants note that the supplemental Information Disclosure Statement (IDS) submitted on February 21, 2007 was not acknowledged in the instant Office Action. The applicants reviewed the status of the subject application on the U.S. Patent Office's Patent Application Information Retrieval (PAIR) system and verified that the Patent Office has received the supplemental IDS. The applicants respectfully request that the Examiner consider the references listed on the Form PTO/SB/08 and make their consideration of record in the subject application.

By this amendment, the applicants have amended the specification at page 16, lines 21-32 through page 17, lines 1-16 to include the correct accession number and sequences of human IFN- $\gamma$ . Recitation of Accession No. NM\_000639 (and the nucleic acid sequence associated therewith) represent an obvious typographical error. Accession No. NM\_00619 provides the nucleotide sequence for the human IFN- $\gamma$ , as would be appreciated by one of ordinary skill in the art. The undersigned avers that no new matter is introduced by this amendment.

Claims 20, 21, 23-31, 54-58, 67, and 68 have been rejected under 35 U.S.C. §103(a) as being obvious over Hogan *et al.* (*Eur. J. Immunol.*, 1998, 28:413-423), in view of Li *et al.* (*J. Immunol.*, 1996, 157:3216-3219), Dow *et al.* (U.S. Patent No. 6,693,086), and O'Donnell *et al.* (*J. Immunol.*, 1999, 163:4246-4252). The applicants respectfully submit that the claimed invention is not obvious in view of the cited references.

When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be non-obvious. *KSR International Co. v. Teleflex Inc.*, 550 U.S. \_\_ 2007, citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966). The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. *Id.* In this case, the references would not be combined by a person of ordinary skill in the art, where the references teach away from each other.

For example, the Hogan *et al.* publication (see page 418-419, last paragraph to beginning of page 419) states “although the protective effects of IL-12 were apparently mediated via the activity of endogenous IFN-gamma, in our study, the use of the former may nevertheless represent a superior approach to vector-directed gene therapy of allergy. We have found that gene transfer of IFN-gamma was far less protective against disease in this model (unpublished data) possibly because of the short half-life of the factor....” Hence, a person of ordinary skill in the art would not combine Hogan *et al.* with any of the cited references where the references teach away from each other. In addition, the applicants reiterate the same arguments previously made with reference to Hogan *et al.*.

Moreover, Hogan *et al.* transfers IL-12 through a vaccinia virus vector, unlike Li *et al.*, which uses liposomal mediated plasmid transfer of interferon-gamma. Hogan *et al.* and Li *et al.* employ very different methods of gene transfer.

Furthermore, Dow *et al.* teaches away from the composition of the claims, as currently amended. Dow *et al.* states that “traditional naked DNA delivery, which has been touted as having an adjuvant effect, is far less effective than the present compositions at stimulating a non-antigen specific immune response (see column 12, lines 13-17). By contrast, the background of the application notes that the “direct effects of these cytokine plasmids as genetic adjuvants in the allergen vaccines used for AIT have not been addressed.” (page 2, lines 12-13). Furthermore, like the Li *et al.* reference, which uses a liposome in one example, Dow *et al.* employs the same, and teaches away from using viral vectors used by Hogan *et al.* by noting that “unlike many protocols for administration of viral vector-based genetic vaccines, the present method can be used to repeatedly deliver the therapeutic composition described herein without consequences associated with some non-specific arms of the immune response, such as the complement cascade (column 12, lines 18-22).

In addition, the O'Donnell *et al.* publication merely observes that intravesical co-administration of BCG plus rIL-12 augments urinary IFN- $\gamma$  production more strongly than either single agent alone, providing an immunological basis for using exogenous IL-12 in conjunction with BCG for bladder cancer immunotherapy. This observed increase in endogenous IFN- $\gamma$  production upon co-administration of IL-12 and antigen does not provide a reasonable expectation of success in increasing Th1-type cytokine production and decreasing Th2-type cytokine production by administering a plasmid encoding nucleic acid sequences encoding human IL-12 and human IFN- $\gamma$ .

With regard to claim 68, the combination of references would not necessarily produce the same predictable results. For example, the Hogan *et al.* reference (see page 415, last paragraph, to page 416, first line) notes that treated mice had IgG2a antibody levels that were similar to those found in controls. This is different from the composition claimed in claim 68, wherein one of the effects is to increase IgG2a. Thus, claims 54-58, and 68 are non-obvious over the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Claims 2-4, 6-8, 45-48, and 50 have been rejected under 35 U.S.C. §112, first paragraph, as claiming new matter. Claims 2 and 4 have been cancelled. Claims 3, 6, 7, 8, 45-48, and 50 have been amended. Accordingly, this rejection under 35 U.S.C. §112, first paragraph, is rendered moot.

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, 43-50, and 52-68 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claimed invention, as currently amended, is fully enabled by the specification.

Claims 1 and 43 have been amended to recite “...nucleic acid sequence encoding p35 and p40 subunits of human IL-12...” Thus, the claims as amended encompass an expression vector that is operable and encodes the p35 and p40 subunits of human IL-12. In addition, the claims as amended encompass a promoter that is operably linked to the gene of interest. Moreover, the claims as amended encompass encoding amino acid sequences that have the biological activity of IL-12 and IFN-γ and thus, results in the Ig and cytokine expression profile claimed.

As the court in *Liebel* recently stated, a “specification need not necessarily describe how to make and use every embodiment of the invention, because the artisan’s knowledge of the prior art and routine experimentation can often fill in gaps.” *Liebel-Flarsheim Co. v. Medrad*, WL 851205 at \*8 (Fed. Cir. 2007), citing *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Nevertheless, numerous preferred examples of administration are taught in the specification and administration is not necessarily unpredictable.

In addition to intramuscular administration and subcutaneous injection, the specification teaches other forms of administration. For example, page 12, third paragraph, of the specification incorporates U.S. Patent No. 6,489,306 by reference, which describes an example of intranasal administration that may be utilized to administer the nucleic acid sequences claimed in this application. Thus, the applicants need not describe every administration route.

Nevertheless, many references describe successful administration routes in immunology. Roy, in U.S. Patent No. 6,475,995, on column 2, lines 46-49, has noted that *successful immunization* has been demonstrated with administration of plasmid DNA by *intramuscular, intradermal, intravenous and subcutaneous* routes. Wahren and Lu, in their review article, *DNA Vaccines: An Overview*, page 4, last paragraph, have noted that DNA vaccines have been delivered by a variety of routes. Felgner, in U.S. Patent No. 6,710,035, describes many routes of administering plasmids encoding immunogenic peptides which include *intramuscular, intravenous, intranasal, subcutaneous, and intradermal* routes (column 23, line 60 to column 24, lines 1-4; Examples 15-18;

and claims 12-17, for example). Thus, a person of ordinary skill in the art would be able to use well-known successfully used gene delivery routes for immunotherapy.

With regard to the cited references, Van Drunen Littel van den Hurk *et al.* notes that cytokine co-administration might enhance the efficacy of DNA vaccines (see page 119, second paragraph). Scheerlinck also notes that it is clear that cytokines... can be used to modulate DNA vaccines (see page 2653, concluding remarks, first three lines). Although the Examiner cites Gautam *et al.* for the proposition that various barriers to delivery exist, nothing in the Gautam *et al.* reference mentions the use of cytokines for promoting enhanced delivery, where the naked DNA itself includes cytokine nucleotide sequences.

Yang is focused on gene therapy in the cardiovascular system, and has limited relevance to the claimed invention. For example, the cited discussion, regarding problems associated with passive diffusion catheters and poor control of delivery to cells of targeted vessels does not apply. Moreover, Yang notes that most investigations about the imaging of gene therapy involve non-cardiovascular systems, which include the subject matter of the current application (see page 36, fifth paragraph).

With regard to the method of delivery, claims 1 and 43 have been amended to recite the term "co-administering." Support for this amendment can be found at page 5, lines 17-25, and page 8, lines 5-8, of the specification. The method of delivering both cytokines is described and enabled by the specification.

The expression profile of the cytokines in the specification represents the full breadth of Th1 type cytokine production and Th2 type cytokine production. For example, at page 31, lines 5-8, of the specification indicates that IL-12 is the primary determinant of Th1 differentiation, and that endogenously synthesized IFN- $\gamma$  both accelerates and enhances the Th1 differentiating effects of IL-12. Copies of the Wenner *et al.* (*J Immunol*, 1996, 156:1442-1447) and Bradley *et al.* (*J Immunol*, 1996, 157:1350-1358) publications, which are cited at page 31 of the subject specification for this premise, are submitted herewith.

Glimcher *et al.*, in U.S. Patent No. 6,399,322, in column 2, lines 13-16, notes that IL-4 promotes the differentiation of Th2 cells while IL-12 and interferon-gamma have the opposite effect. For example, administration of recombinant IL-4 or antibodies to IL-12 ameliorate EAE, a Th1-

driven autoimmune disease, while anti-IL-4 antibodies cure a Th2-mediated parasitic disease, *Leishmania major* (column 2, lines 21-27). However, like the applicants (specification, page 2, lines 5-7), Glimcher *et al.* (column 2, lines 28-32) notes that systemic administration of cytokines or antibodies may have unwanted side effects but concludes that alternative approaches to manipulating Th1/Th2 subsets are still needed, which the subject invention, like the Glimcher *et al.* patent, addresses. Accordingly, the expression profiles of the representative Th1 and Th2 cytokines are predictive of the class of the Th1 and Th2 cytokines, as shown by the examples provided. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, 43-50, and 52-68 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. By this amendment, independent claims 1, 43, and 54 have been amended to make clear that the promoter sequences are operably linked to the nucleic acid sequences encoding the p35 and p40 subunits of human IL-12 and human IFN- $\gamma$ . Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

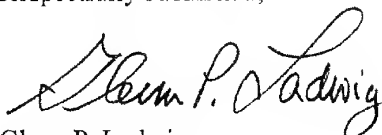
In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.



The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time

Wenner *et al.* (*J Immunol*, 1996, 156:1442-1447)

Bradley *et al.* (*J Immunol*, 1996, 157:1350-1358)

Supplemental Information Disclosure Statement; Form PTO/SB/08; references